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(54) Title: USE OF HIV-PROTEASE INHIBITORS TO BLOCK CELL MIGRATION AND/OR INVASION, TISSUE INFILTRATION AND OEDEMA FORMATION

(57) Abstract: The present invention relates to a method to block the invasion of normal, neoplastic inflammatory or immune cells, tissue infiltration, and/or oedema formation through inhibition or modulation of molecules and proteolytic enzymes such as -but not exclusively- MMPs, for the therapy of all diseases whose pathogenesis is related to the above processes, including tumours, non-neoplastic angioproliferative diseases, inflammatory diseases, or autoimmune diseases, the method being based on the use of inhibitors of the protease of the HIV virus (HIV-PI).

AMENDED CLAIMS

[received by the International Bureau on 19 December 2002 (19.12.02)
Claims 1-27 replaced by new claims 1-26

CLAIMS - Art. 19PCT

1. Use of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI, for the preparation of a medicament for treating a subject suffering from or susceptible to a condition which can be treated or prevented by blocking the migration/invasion of cells selected in the group of: endothelial, neoplastic, inflammatory or immune cells.
2. Use according to claim 1 wherein cell migration/invasion results in tissue infiltration and/or oedema formation.
3. Use according to claims 1-2 wherein the block is obtained through inhibition or modulation of molecules and proteolytic enzymes selected in the group of: MMPs including MMP-2, stromelysins and matrilysin; enzymes activating MMPs; thrombospondin; bFGF and VEGF alone or associated between them, Tat alone or in the presence of bFGF.
4. Use according to claim 3 in which the proteolytic enzymes are MMPs.
5. Use according to claims 1-4 wherein the condition to be treated or prevented is at least one of the following pathologies: inflammatory, autoimmune, neoplastic, non-neoplastic angioproliferative diseases.
6. Use according to claims 1-6 wherein the HIV-PI has an anti-angiogenic, anti-tumour, anti-oedemigenic and/or anti-inflammatory activity for the treatment of KS, tumours and non-neoplastic angioproliferative, inflammatory and autoimmune diseases.
7. Use according to claims 1-6 wherein the HIV-PI is selected among the following compounds: indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, lopinavir and ritonavir, corresponding pharmaceutically acceptable derivatives and chemical analogues, and mixtures thereof.
8. Use according to claim 7 wherein the compounds are administered at the following doses: indinavir: 600 mg/day, 1200 mg/day, 2400 mg/day and 4800 mg/day; saquinavir: 900 mg/day; 1800 mg/day, 3600 mg/day, 7200 mg/day
9. Use according to claims 1-8 wherein the pathological condition is selected in the group of: Kaposi's sarcoma, angiogenesis; non-neoplastic angioproliferative diseases of eye, kidney, vascular system, skin, such as, for example, diabetic retinopathy, retrolental fibroplasia, trachoma, vascular

glaucoma, psoriasis, immune and non-immune inflammation, atherosclerosis, keloids; benign and malignant tumours of the soft tissues, the cartilages, the bones and the blood; autoimmune diseases in general, in particular systemic lupus erythematosus, scleroderma, rheumatoid arthritis, psoriasis, thyroiditis, ulcerous rectocolitis and Crohn's disease, Goodpasture's syndrome, systemic vasculitis, Sjögren's syndrome, primitive biliary cirrhosis; inflammatory diseases, in particular chronic inflammation associated with allergies and with viral infective, bacterial or parasitic agents, including the Castleman's multicentric disease.

10. Use according to claim 9 wherein the HIV-PI is in association with anti-inflammatory, anti-angiogenic or anti-tumour drugs.

11. Use according to claims 1-10 in subjects infected or not infected by HIV.

12. Use according to claims 1-11 wherein the drug is administered according to a procedure selected among; oral, intravenous, intramuscular, subcutaneous, intradermal, intraperitoneal, intrathecal, intrapleural, intrauterine, transmucosal, rectal, vaginal, intralesional or percutaneous administration.

13. Method for modulating biological processes involving cell migration and invasion, tissue infiltration and activity of molecules involved in these cell pathways, including MMPs and thrombospondin, said method comprising the administration of an effective amount of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI.

14. Method for treating pathological conditions involving cell migration and invasion, tissue infiltration and activity of molecules involved in these cell pathways, including MMPs and thrombospondin, said method comprising the administration of a therapeutically effective amount of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI.

15. Method for treating a subject suffering from or susceptible to a condition which can be treated or prevented by blocking the migration/invasion of cells selected in the group of: endothelial, neoplastic, inflammatory or immune cells, said method comprising the administration of a therapeutically effective amount of at least one compound selected in the group of the inhibitors of the protease of the HIV virus, HIV-PI.

16. Method according to claim 15 wherein cell migration/invasion results in tissue infiltration and/or oedema formation.

17. Method according to claim 15 wherein the block is obtained through inhibition or modulation of molecules and proteolytic enzymes selected in the group of: MMPs including MMP-2, stromelysins and matrilysin; enzymes activating MMPs; thrombospondin; bFGF and VEGF alone or associated between them, Tat alone or in the presence of bFGF.

18. Method according to claim 17 wherein the proteolytic enzymes are MMPs.

19. Method according to claim 15 wherein the condition to be treated or prevented is at least one of the following pathologies: inflammatory, autoimmune, neoplastic, non-neoplastic angioproliferative diseases.

20. Method according to claim 15 wherein the HIV-PI has an anti-angiogenic, anti-tumour, anti-oedemigenic and/or anti-inflammatory activity for the treatment of KS, tumours and non-neoplastic angioproliferative, inflammatory and autoimmune diseases.

21. Method according to claim 15 wherein the HIV-PI is selected among the following compounds: indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, lopinavir and ritonavir, corresponding pharmaceutically acceptable derivatives and chemical analogues, and mixtures thereof.

22. Method according to claim 21 wherein the compounds are administered at the following doses: indinavir: 600 mg/day, 1200 mg/day, 2400 mg/day and 4800 mg/day; saquinavir: 900 mg/day; 1800 mg/day, 3600 mg/day, 7200 mg/day

23. Method according to claim 15 wherein the pathological condition is selected in the group of: Kaposi's sarcoma, angiogenesis; non-neoplastic angioproliferative diseases of eye, kidney, vascular system, skin, such as, for example, diabetic retinopathy, retrolental fibroplasia, trachoma, vascular glaucoma, psoriasis, immune and non-immune inflammation, atherosclerosis, keloids; benign and malignant tumours of the soft tissues, the cartilages, the bones and the blood; autoimmune diseases in general, in particular systemic lupus erythematosus, scleroderma, rheumatoid arthritis, psoriasis, thyroiditis, ulcerous rectocolitis and Crohn's disease, Goodpasture's syndrome, systemic vasculitis, Sjögren's syndrome, primitive biliary cirrhosis; inflammatory

diseases, in particular chronic inflammation associated with allergies and with viral infective, bacterial or parasitic agents, including the Castleman's multicentric disease.

24. Method according to claim 15 wherein the HIV-PI is in association with anti-inflammatory, anti-angiogenic or anti-tumour drugs.

25. Method according to claim 15 wherein the subjects are subjects infected or not infected by HIV.

26. Method according to claim 15 wherein the drug is administered according to a procedure selected among; oral, intravenous, intramuscular, subcutaneous, intradermal, intraperitoneal, intrathecal, intrapleural, intrauterine, transmucosal, rectal, vaginal, intralesional or percutaneous administration.